

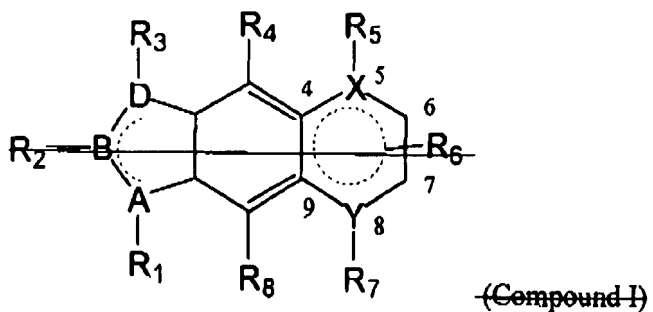
In re Application of: Levitzki et al
Serial No.: 10/715,547
Filed: November 19, 2003
Office Action Mailing Date: April 16, 2007

Examiner: Tamthom N. Truong
Group Art Unit: 1624
Attorney Docket: 27148

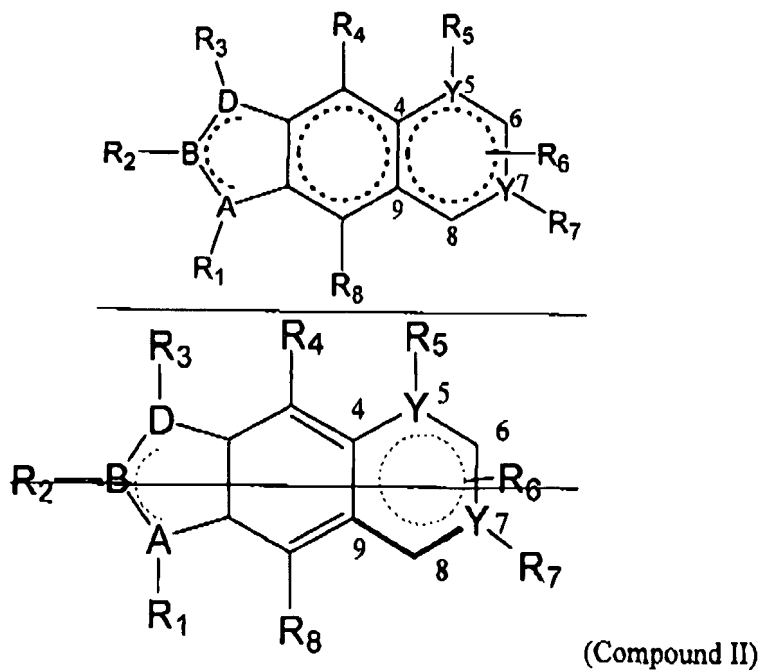
In the claims:

Please amend the claims as follows:

1. (Currently Amended) A ~~preparation of a purified~~ tyrphostin isomer comprising a compound of a general formula:



or



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wherein,

4, 5, 6, 7, 8 and 9 indicate positions on a terminal 6-member ring;

A, D and Y are each a nitrogen;

B is a carbon;

A, B, D, X and Y are each independently selected from the group consisting of carbon, nitrogen, oxygen and sulfur;

R₁, R₂, R₃, R₅ and R₇ are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, hydroxy, alkoxy, halo, C-carboxy, O-carboxy, carbonyl, thiocarbonyl, C-amido, guanlyguanyl, sulfonyl, trihalomethane-sulfonyl and a pair of electrons, or alternatively, R₁ and R₂ or R₂ and R₃ form a 5-7 member ring structure;

R₆ is selected from the group consisting of alkyl, trihaloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, ~~hydroxy~~, alkoxy, aryloxy, thiohydroxy, thioalkoxy, thioaryloxy, sulfinyl, sulfonyl, N-sulfonamido, S-sulfonamido, trihalomethylsulfonamido, carbonyl, thiocarbonyl, C-carboxy, O-carboxy, C-amido, N-amido, cyano, nitro, halo, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, ureido, guanyl, guanidino, amino and a physiologically acceptable salt ~~or a prodrug~~ thereof;

R₄ and R₈ are each independently selected from the group consisting of hydrogen, alkyl, trihaloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, thiohydroxy, thioalkoxy, thioaryloxy, sulfinyl, sulfonyl, N-sulfonamido, S-sulfonamido, trihalomethylsulfonamido, carbonyl, thiocarbonyl, C-carboxy, O-carboxy, C-amido, N-amido, cyano, nitro, halo, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, ureido, guanyl, guanidino, amino and -NR₁₀R₁₁ and, a physiologically acceptable salt ~~or a prodrug~~ thereof;

R₁₀ and R₁₁ are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, carbonyl and sulfonyl, or alternatively R₁₀ and R₁₁

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form a five- or six-member heteroalicyclic ring; and, a physiologically acceptable salt or a prodrug thereof;

whereas, ~~for Compound I, said preparation is enriched either for R₆ at position 6 or for R₆ at position 7, or, for Compound II, said preparation is enriched either for R₆ at position 6 or for R₆ at position 8.~~

2. (Currently Amended) The purified tyrphostin isomer preparation of claim 1, wherein

~~A, D, X and Y are each a nitrogen;~~

~~B is a carbon;~~

R₁ and R₂ are each independently selected from the group consisting of alkyl, alkoxy, halogen, nitro and amine group;

R₃, R₅ and R₇ are each a pair of electrons;

R₆ is an aryl, selected from the group consisting of phenyl, ferrocene, thiophene, furane, pyrrole, indole, thiazole, imidazole and pyridine.

3. (Currently Amended) The purified tyrphostin isomer preparation of claim 2, wherein

R₁ and R₂ are each a methyl;

R₄ and R₈ are each a hydrogen.

4. (Withdrawn) The preparation of claim 1, wherein said preparation is enriched for Compound I in which R₆ is at position 6.

5. (Withdrawn) The preparation of claim 1, wherein said preparation is enriched for Compound I in which R₆ is at position 7.

6-8. (Canceled)

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9. (Currently Amended) A pharmaceutical composition comprising, as an active ingredient, the purified tyrphostin isomer preparation of claim 1 and a pharmaceutically acceptable carrier.

10. (Original) The pharmaceutical composition of claim 9, wherein said pharmaceutically acceptable carrier is a slow release carrier.

11. (Original) The pharmaceutical composition of claim 10, wherein said slow release carrier is polylactic acid.

12. (Withdrawn) A method of treating or preventing a protein tyrosine kinase related disorder in an organism, the method comprising the step of administering to said organism a therapeutically effective amount of the pharmaceutical composition of claim 9.

13. (Withdrawn) The method of claim 12, wherein said protein tyrosine kinase related disorder is selected from the group consisting of an EGF related disorder, a PDGF related disorder, an IGF related disorder and a met related disorder.

14. (Withdrawn) The method of claim 12, wherein said protein tyrosine kinase related disorder is selected from the group consisting of a cell proliferative disorder, a fibrotic disorder and a metabolic disorder.

15. (Withdrawn) The method of claim 14, wherein said cell proliferative disorder is selected from the group consisting of papilloma, blastoglioma, Kaposi's sarcoma, melanoma, lung cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, astrocytoma, head cancer, neck cancer, bladder cancer, breast cancer, lung cancer, colorectal cancer, thyroid cancer, pancreatic cancer, gastric cancer, hepatocellular carcinoma, leukemia, lymphoma, Hodgkin's disease, Burkitt's disease,

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arthritis, rheumatoid arthritis, diabetic retinopathy, angiogenesis, restenosis, in-stent restenosis, vascular graft restenosis.

16. (Withdrawn) The method of claim 14, wherein said cell fibrotic disorder is selected from the group consisting of pulmonary fibrosis, hepatic cirrhosis, atherosclerosis, glomerulonephritis, diabetic nephropathy, thrombic microangiopathy syndromes, transplant rejection.

17. (Withdrawn) The method of claim 14, wherein said cell metabolic disorder is selected from the group consisting of psoriasis, diabetes, wound healing, inflammation, and neurodegenerative diseases.

18. (Withdrawn) The method of claim 12, wherein said protein tyrosine kinase related disorder is selected from the group consisting of papilloma, blastoglioma, Kaposi's sarcoma, melanoma, lung cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, astrocytoma, head cancer, neck cancer, bladder cancer, breast cancer, small-cell lung cancer, colorectal cancer, thyroid cancer, pancreatic cancer, gastric cancer, hepatocellular carcinoma, leukemia, lymphoma, Hodgkin's disease, Burkitt's disease, psoriasis, pulmonary fibrosis, arthritis, rheumatoid arthritis, diabetic retinopathy, restenosis, in-stent restenosis, vascular graft restenosis, hepatic cirrhosis, atherosclerosis, angiogenesis, glomerulonephritis, diabetic nephropathy, thrombic microangiopathy syndromes, transplant rejection, autoimmune disease, wound healing, inflammation, neurodegenerative diseases, diabetes and hyperimmune disorders.

19. (Withdrawn) The method of claim 12, wherein said organism is a mammal.

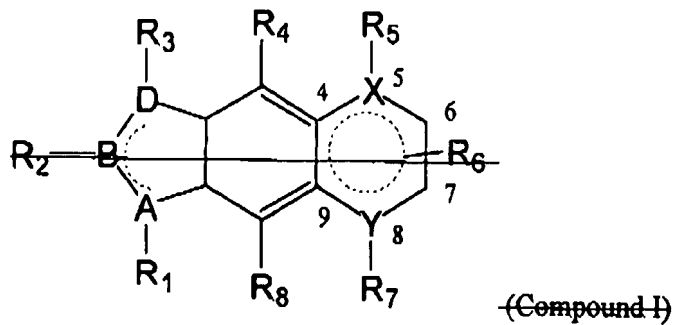
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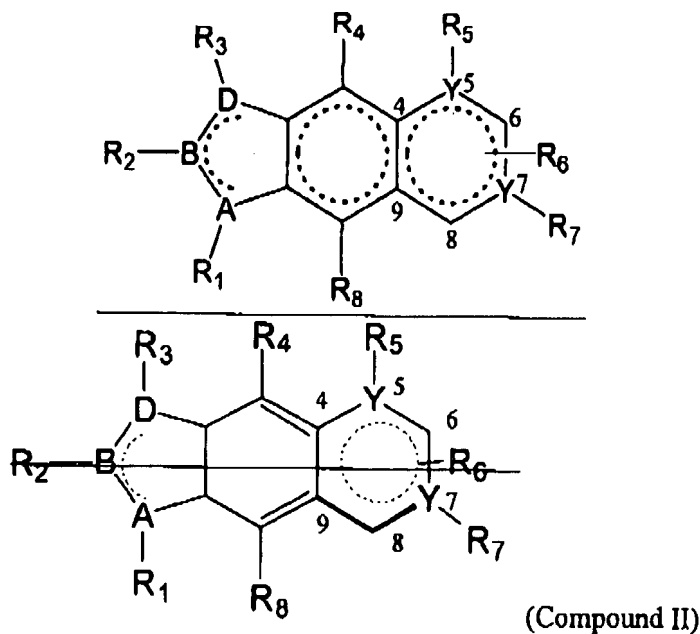
20. (Withdrawn) The method of claim 19, wherein said mammal is a human.
21. (Withdrawn) A method of locally treating or preventing a disorder of a tissue of an organism comprising the step of locally applying the pharmaceutical composition of claim 9 onto said tissue.
22. (Withdrawn) The method of claim 21, wherein said organism is a human.
23. (Withdrawn) The method of claim 21, wherein said tissue is selected from the group consisting of blood vessel, lung and skin.
24. (Withdrawn) A method of inhibiting cell proliferation comprising the step of subjecting the cells to the tyrphostin preparation of claim 1.
25. (Withdrawn) The method of claim 24, wherein said cells are of an organism, whereas subjecting the cells to said preparation is effected *in vivo*.
26. (Withdrawn) The method of claim 25, wherein said organism is a human.
27. (Withdrawn) The method of claim 24, wherein subjecting the cells to said preparation is effected *in vitro*.
28. (Currently Amended) A method of enriching ~~a preparation of tyrphostins~~, for a specific ~~geometrical isomer~~, ~~the preparation comprising a compound~~ a tyrphostin of a general formula:

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or



wherein,

4, 5, 6, 7, 8 and 9 indicate positions on a terminal 6-member ring;

A, D and Y are each a nitrogen;

B is a carbon;

~~A, B, D, X and Y are each independently selected from the group consisting of carbon, nitrogen, oxygen and sulfur;~~

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R_1 , R_2 , R_3 , R_5 and R_7 are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, hydroxy, alkoxy, halo, C-carboxy, O-carboxy, carbonyl, thiocarbonyl, C-amido, ~~guanylyl~~ guanyl, sulfonyl, trihalomethane-sulfonyl and a pair of electrons, or alternatively, R_1 and R_2 or R_2 and R_3 form a 5-7 member ring structure;

R_6 is selected from the group consisting of alkyl, trihaloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, thiohydroxy, thioalkoxy, thioaryloxy, sulfinyl, sulfonyl, N-sulfonamido, S-sulfonamido, trihalomethylsulfonamido, carbonyl, thiocarbonyl, C-carboxy, O-carboxy, C-amido, N-amido, cyano, nitro, halo, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, ureido, guanyl, guanidino, amino and a physiologically acceptable salt ~~or a prodrug~~ thereof;

R_4 and R_8 are each independently selected from the group consisting of hydrogen, alkyl, trihaloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, thiohydroxy, thioalkoxy, thioaryloxy, sulfinyl, sulfonyl, N-sulfonamido, S-sulfonamido, trihalomethylsulfonamido, carbonyl, thiocarbonyl, C-carboxy, O-carboxy, C-amido, N-amido, cyano, nitro, halo, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, ureido, guanyl, guanidino, amino and $-NR_{10}R_{11}$ and, a physiologically acceptable salt ~~or a prodrug~~ thereof;

R_{10} and R_{11} are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, carbonyl and sulfonyl, or alternatively R_{10} and R_{11} form a five- or six-member heteroalicyclic ring; and, a physiologically acceptable salt ~~or a prodrug~~ thereof;

whereas, for each molecule of ~~Compound I~~, ~~R_6 is at position 6 or 7, or, for~~
~~each molecule of Compound II~~, R_6 is at position 6 or 8;

the method comprising the steps of:

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- (a) chromatographing ~~said a preparation of the tyrphostin~~ through a matrix, thereby separating isomers in said preparation;
- (b) collecting at least one specific isomer.

29. (Original) The method of claim 28, further comprising the step of:

- (c) crystallizing said at least one specific isomer.

30. (Currently amended) The method of claim 28, wherein

~~A, D, X and Y are each a nitrogen;~~

~~B is a carbon;~~

R₁ and R₂ are each independently selected from the group consisting of alkyl, alkoxy, halogen, nitro and amine group;

R₃, R₅ and R₇ are each a pair of electrons;

R₆ is an aryl, selected from the group consisting of phenyl, ferrocene, thiophene, furane, pyrrole, indole, thiazole, imidazole and pyridine.

31. (Original) The method of claim 30, wherein

R₁ and R₂ are each a methyl;

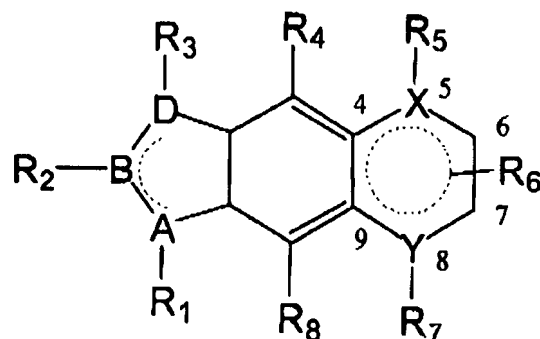
R₄ and R₈ are each a hydrogen.

32. (Withdrawn) A method for preparing a pharmaceutical composition for slow release of a tyrphostin comprising the steps of:

- (a) providing an isomer-enriched tyrphostin preparation comprising a compound of a general formula:

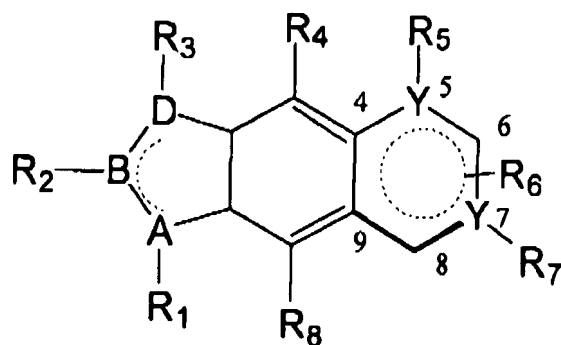
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(Compound I)

or



(Compound II)

wherein,

4, 5, 6, 7, 8 and 9 indicate positions on a terminal 6-member ring;

A, B, D, X and Y are each independently selected from the group consisting of carbon, nitrogen, oxygen and sulfur;

R₁, R₂, R₃, R₅ and R₇ are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, hydroxy, alkoxy, halo, C-carboxy, O-carboxy, carbonyl, thiocarbonyl, C-amido, guanly, sulfonyl, trihalomethane-sulfonyl and a pair of electrons, or alternatively, R₁ and R₂ or R₂ and R₃ form a 5-7 member ring structure;

R₆ is selected from the group consisting of alkyl, trihaloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, , heteroaryl, , heteroalicyclic, hydroxy, alkoxy, aryloxy,

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thiohydroxy, thioalkoxy, thioaryloxy, sulfinyl, sulfonyl, N-sulfonamido, S-sulfonamido, trihalomethylsulfonamido, carbonyl, thiocarbonyl, C-carboxy, O-carboxy, C-amido, N-amido, cyano, nitro, halo, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, ureido, guanyl, guanidino, amino and a physiologically acceptable salt or a prodrug thereof;

R₄ and R₈ are each independently selected from the group consisting of hydrogen, alkyl, trihaloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, thiohydroxy, thioalkoxy, thioaryloxy, sulfinyl, sulfonyl, N-sulfonamido, S-sulfonamido, trihalomethylsulfonamido, carbonyl, thiocarbonyl, C-carboxy, O-carboxy, C-amido, N-amido, cyano, nitro, halo, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, ureido, guanyl, guanidino, amino and -NR₁₀R₁₁ and, a physiologically acceptable salt or a prodrug thereof;

R₁₀ and R₁₁ are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, carbonyl and sulfonyl, or alternatively R₁₀ and R₁₁ form a five- or six-member heteroalicyclic ring; and, a physiologically acceptable salt or a prodrug thereof;

whereas, for Compound I, said preparation is enriched either for R₆ at position 6 or for R₆ at position 7, or, for Compound II, said preparation is enriched either for R₆ at position 6 or for R₆ at position 8;

(b) dissolving or dispersing a slow release carrier and said isomer-enriched tyrphostin preparation in an organic solvent for obtaining an organic solution containing said carrier and said isomer-enriched tyrphostin preparation;

(c) adding said organic solution into an aqueous solution for obtaining an oil-in-water-type emulsion; and

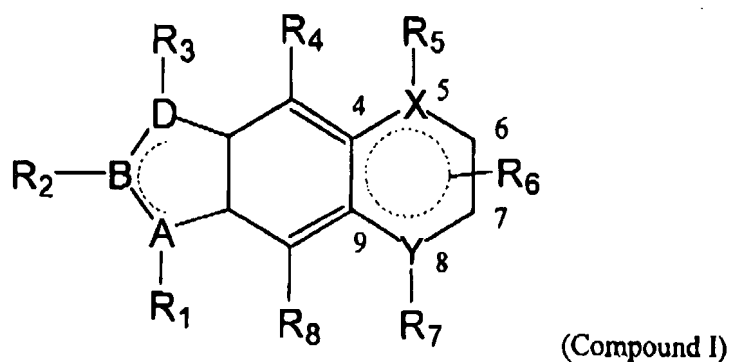
(d) evaporating said organic solvent from said oil-in-water-type emulsion for obtaining a colloidal suspension of particles containing said slow release carrier and said isomer-enriched tyrphostin preparation.

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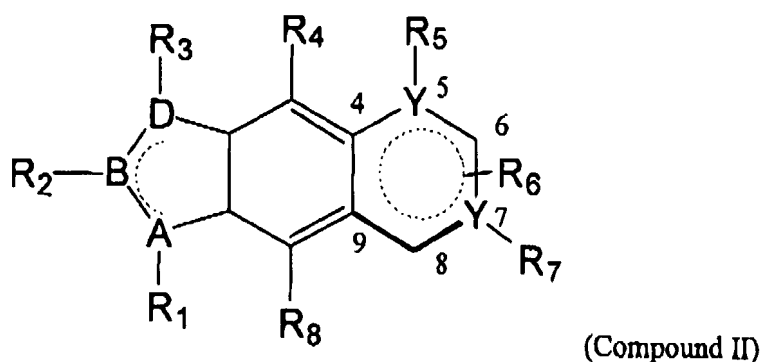
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33. (Withdrawn) The method of claim 32, wherein said slow release carrier is polylactic acid.

34. (Withdrawn) A stent comprising a substantially tubular body, the body is made of a material designed for slow release of a tyrphostin preparation, said tyrphostin preparation including a compound of a general formula:



or



wherein,

4, 5, 6, 7, 8 and 9 indicate positions on a terminal 6-member ring;

A, B, D, X and Y are each independently selected from the group consisting of carbon, nitrogen, oxygen and sulfur;

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R_1 , R_2 , R_3 , R_5 and R_7 are each independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, hydroxy, alkoxy, halo, C-carboxy, O-carboxy, carbonyl, thiocarbonyl, C-amido, guanly, sulfonyl, trihalomethane-sulfonyl and a pair of electrons, or alternatively, R_1 and R_2 or R_2 and R_3 form a 5-7 member ring structure;

R_6 is selected from the group consisting of alkyl, trihaloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, thiohydroxy, thioalkoxy, thioaryloxy, sulfinyl, sulfonyl, N-sulfonamido, S-sulfonamido, trihalomethylsulfonamido, carbonyl, thiocarbonyl, C-carboxy, O-carboxy, C-amido, N-amido, cyano, nitro, halo, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, ureido, guanyl, guanidino, amino and a physiologically acceptable salt or a prodrug thereof;

R_4 and R_8 are each independently selected from the group consisting of hydrogen, alkyl, trihaloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, thiohydroxy, thioalkoxy, thioaryloxy, sulfinyl, sulfonyl, N-sulfonamido, S-sulfonamido, trihalomethylsulfonamido, carbonyl, thiocarbonyl, C-carboxy, O-carboxy, C-amido, N-amido, cyano, nitro, halo, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, ureido, guanyl, guanidino, amino and $-NR_{10}R_{11}$ and, a physiologically acceptable salt or a prodrug thereof;

R_{10} and R_{11} are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, carbonyl and sulfonyl, or alternatively R_{10} and R_{11} form a five- or six-member heteroalicyclic ring; and, a physiologically acceptable salt or a prodrug thereof;

whereas, for Compound I, said preparation is enriched either for R_6 at position 6 or for R_6 at position 7, or, for Compound II, said preparation is enriched either for R_6 at position 6 or for R_6 at position 8.